

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellant: Frank A. Skraly

Serial No.: 10/661,939

Art Unit: 1652

Filed: September 12, 2003

Examiner: Iqbal Hussain Chowdhury

For: *POLYHYDROXYALKANOATE PRODUCTION BY COENZYME
A-DEPENDENT ALDEHYDE DEHYDROGENASE PATHWAYS*

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

APPEAL BRIEF

Sir:

This is an appeal from the final rejection of claims 16-23 in the Office Action mailed November 29, 2006, in the above-identified patent application. A Notice of Appeal was filed on April 27, 2007, with a two months extension of time. The Commissioner is hereby authorized to charge \$500.00, the fee for the filing of this Appeal Brief for a large entity to Deposit Account No. 50-3129.

It is believed that no additional fee is required with this submission. However, should an additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-3129

(1) REAL PARTY IN INTEREST

The real party in interest of this application is the assignee, Metabolix, Inc., Cambridge, MA.

(2) RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences known to appellant, the undersigned, or appellant's assignee which directly affects, which would be directly affected by, or which would have a bearing on the Board's decision in this appeal.

(3) STATUS OF CLAIMS

Claims 16-23 are pending, rejected, and on appeal. Claims 13-15 and 36-37 have been cancelled. Claims 1-12 and 24-35 are pending and have been withdrawn from examination. Product claims 16-23 were elected without traverse on February 13, 2006, in response to a restriction requirement mailed on January 11, 2006, with the understanding that withdrawn process (method) claims (1-12 and 24-35) that depend from or recite all the limitations of the product claims would be rejoined. Claims 13-15 and 36-38 drawn to a PHA polymer were cancelled. The text of each claim on appeal, as pending, is set forth in an Appendix to this Appeal Brief.

(4) STATUS OF AMENDMENTS

The claims were last amended in an Amendment and Response filed on September 14, 2006. No amendment was filed after the final office action.

(5) SUMMARY OF CLAIMED SUBJECT MATTER

Independent claim 16 defines a recombinant organism selected from the group consisting of bacteria, yeast, fungi and plants for producing polyhydroxyalkanoates, comprising a heterologous gene encoding a CoA-dependent aldehyde dehydrogenase and a PHA synthase (see page 4, lines 5-9, page 7, lines 23-25 and page 11, lines 10-16). Dependent claim 17 requires the

recombinant organism of claim 16 to further comprise a heterologous gene encoding a PHA synthase. The organisms can further comprise one or more genes, wherein the genes encode enzymes selected from the group consisting of acyl-CoA transferase, acyl-CoA synthetase, β -ketothiolase, acetoacetyl-CoA reductase as defined by claim 18 and as defined by claim 20, one or more of these genes are heterologous to the recombinant organism (see page 4, lines 5-9). As defined by claim 19, one or more of the genes are endogenous to the recombinant organism (see page 5, lines 8-9). Claim 21 defines the organism of claim 16 wherein the gene is *eutE* of *E. coli* (see page 9, lines 17-18). Claims 22 and 23 define the recombinant organism of claim 16 to be a bacteria or a plant respectively (see page 11, lines 15-16).

(6) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The issues presented on appeal are:

(1) whether claims 16-23 meet the written description requirement of 35 U.S.C. § 112, first paragraph.

(2) whether claims 16-23 are enabled as required by 35 U.S.C. § 112, first paragraph.

(7) ARGUMENTS

(i) The claimed organisms

Polyhydroxyalkanoates (PHAs) are natural, thermoplastic polyesters and can be processed by traditional polymer techniques for use in an enormous variety of applications, including consumer packaging, disposable diaper linings and garbage bags, food and medical products. The enzymes in the polyhydroxybutyrate (PHB) biosynthetic pathway occurring naturally in bacteria were elucidated and used to engineer other bacteria and plants, as described

in the background of the invention in the application.

PHA copolymers containing 3-hydroxyvalerate (3HV) have been available commercially and have proven useful in a range of applications. These have been produced using bacteria fed appropriate six carbon substrates. In some cases, copolymers with a 3HV level of around 3-12% by weight copolymer are required. In other cases, a 3HV level of 15-30% by weight is more useful. These higher levels are achieved by increasing the level of propionic acid in the feed. However, propionic acid is toxic to the cell, reducing the rate of growth and polymer production, with associated increases in the cost of production, which are significant. Furthermore, conversion of other co-feed such as 1-propanol or propylene glycol to PHA occurs via propionaldehyde, which may then be converted to propionic acid.

Appellants have discovered a method for overcoming this drawback of propionic acid toxicity, by providing recombinant organisms which not only express the genes necessary for the production of PHA which may include hydroxyhexanoate monomers, but also express a CoA-dependent aldehyde dehydrogenase, which can convert the propionaldehyde intermediate directly to propionyl-CoA. This not only prevents the accumulation of toxic levels of propionic acid in the cells, it also eliminates the need for an additional CoA synthetase or transferase that would have been necessary to convert the propionic acid to the fatty acyl intermediate which is the substrate for PHA synthase.

(ii) Rejection under 35 U.S.C. § 112, first paragraph, written description

Claims 16-23 were rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the art that the inventor had possession of the claimed invention.

The Legal Standard

The general standard for the written description requirement is that "a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention." See M.P.E.P. § 2163:

"The courts have described the essential question to be addressed in a variety of ways. An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). This standard was phrased in *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), whether an applicant has conveyed with reasonable clarity to those skilled in the art that, as of the filing date sought, that he or she was in possession of the invention, as claimed. See also *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting *In re Kaslow*, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)).

An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997). Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or

structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. See, e.g., *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997); *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991) (one must define a compound by "whatever characteristics sufficiently distinguish it")."

"The inquiry into whether the description requirement is met must be determined on a case-by-case basis and is a question of fact. *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). A description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption. See, e.g., *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). The examiner, therefore, must have a reasonable basis to challenge the adequacy of the written description. The examiner has the initial burden of presenting by a *preponderance of evidence* why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *Wertheim*, 541 F.2d at 263, 191 USPQ at 97."

All that is required is that the specification provides sufficient description to reasonably convey to those skilled in the art that, as of the filing date sought, the inventor was in possession of the claimed invention. *Union Oil of California v. Atlantic Richfield Co.*, 208 F.3d 989, 997, 54 U.S.P.Q.2d 1227, 1232 (Fed. Cir. 2000); *Vas Cath*, 935 F.2d at 1563-64. An applicant may

show possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. As noted by the Board of Appeals and Interferences, the written description requirement does not require a description of the complete structure of every species within a chemical genus. (*see Utter v. Hiraga*, 845 F.2d 993, 998, 6 U.S.P.Q.2d 1709, 1714 (Fed. Cir. 1988), stating “A specification may, within the meaning of 35 U.S.C. § 112, para. 1, contain a written description of a broadly claimed invention without describing all species that claim encompasses.”).

An adequate written description of the invention may be shown by any description of sufficient, relevant, identifying characteristics so long as a person skilled in the art would recognize that the inventor had possession of the claimed invention. *Id.*, citing *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1323, 56 USPQ2d 1481, 1483 (Fed. Cir. 2000); *Pfaff v. Wells Electronics, Inc.*, 55 U.S. at 66, 119 S.Ct. at 311, 48 USPQ2d at 1646 (1998).

The Board of Patent Appeals and Interferences warned that it is an improper analysis to determine that the claims are directed to an invention which is broader than that which is described in the specification since the written description is determined from the perspective of what the specification conveys to one skilled in the art citing *In re GPAC Inc.*, 57 F.3d 1573, 1579, 35 USPQ2d 1116, 1121 (Fed. Cir. 1995) and *Vas Cath*, 935 F.2d at 1563-64. Thus the Board re-emphasized that the specification need not always spell out every detail; only enough “to convince a person of skill in the art that the inventor possessed the invention and to enable such a person to make and use the invention without undue experimentation.” *LizardTech Inc. v.*

Earth Resource Mapping, Inc., 424 F.3d 1336, 1344-34, 76 USPQ2d 1724, 1732 (Fed. Cir. 2005).

Analysis

Claims 16 and 17

Claims 16 and 17 define a recombinant organism selected from the group consisting of bacteria, yeast, fungi and plants for producing polyhydroxyalkanoates, comprising a heterologous gene encoding a Co-A-dependent aldehyde dehydrogenase and a PHA synthase. It is clear from the disclosure in the specification, that one of ordinary skill in the art would conclude that Appellants were in possession of the claimed organisms, for the reasons set forth below.

The enzymes defined by the claims are well-known, exist within well-defined classes of proteins, and the genes encoding them are known and described in the literature. The words "PHA synthase," and "Co-A-dependent aldehyde dehydrogenase" classify proteins and readily convey distinguishing information concerning identity, via structure and function, such that one of ordinary skill in the art could easily visualize the identity of the members of each classification. It is well known to those of ordinary skill in the art that functional definitions **do** provide structural information commonly possessed by all members of each class, especially as applied to enzymes. Over 30 years ago, Nobel Laureate Christian B. Anfinsen proved that a protein's "knowledge" of how to fold is stored in its sequence of amino acids. It is this fold that determines the protein's functionality (i.e. substrates recognized, reactions catalyzed, targeted protein binding, etc.). Conversely, a particular function can be directly attributed to particular

folds determined by specific, or conserved, sequences of amino acids. It is well established in the art that structure–function relationships do exist, and it is no more prevalent than within families of proteins, such as those that drive the specific reactions of claim 1. The written description requirement can be met by a functional description of claimed materials, if coupled with a known or disclosed correlation between function and structure. A claim is not unpatentable simply because the “embodiments of the specification do not contain examples explicitly covering the full scope of the claim language.” *LizardTech Inc., v. Earth Resource Mapping, Inc.* 424 F.3d at 1343; see also *Union Oil Co. v. Atlantic Richfield Co.*, 208 F.3d 989, 997, 54 USPQ2d 1227, 1232 (Fed. Cir. 2000).

However, not only can one of ordinary skill in the art visualize the identity of the members of the class of enzymes recited in claims 16, and 17, for reasons set forth above, the specification actually describes a representative number of the enzymes in each class. The specification at least from page 9, line 13 until page 10, line 29 provides numerous sources of a CoA-dependent aldehyde dehydrogenase, including accession numbers. As disclosed in the specification at least at page 3, lines 9-12, genes (such as PHA synthase) for the development of recombinant producers are known in the art, citing Madison and Huisman, *Microbiol. Mol. Biol. Rev.*, 63:21-53 (1999) (“Madison”) and International publication No. WO 99/14313 by Metabolix, Inc. (“Huisman”, cited in the information disclosure statement filed on Dec, 23, 2003, and considered by the Examiner on June 15, 2006; copies of which are attached to the evidence appendix). Appellants respectfully point out that the information incorporated from these references is as much a part of the application as filed as if the text was repeated in the

application, and should be treated as part of the text of the application as filed (See MPEP §2163.07(b) not only due to the incorporation by reference but because these references establish what is known and available to those skilled in the art. For example, Madison discloses the amino acid sequences of PHA polymerase from *R. eutropha*, *P. oleovorans*, the *Synechocystis* *sp.*, and *Z. ramigera*. As extensively discussed in Madison, PHA synthase has been isolated from many microorganisms in addition to those mentioned above. Thus, actual DNA can be obtained from the authors of the publications cited for the isolation of the requisite genes, or purchased from commercial suppliers, such as the American Type Culture Collection (ATCC). Published amino acid and nucleotide sequence listings for the various genes can also be obtained from GenBank or the National Center for Biotechnology Information (NCBI). It is clear that the specification does describe the structures of different aldehyde dehydrogenase and PHA synthases.

The courts have affirmed that a description of a genus of DNA's may be achieved by means of recitation of a representative number of DNA's defined by nucleotide sequence, falling within the scope of the genus or a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. This is clearly the case here; Appellants have recited a representative number of DNA's defined by nucleotide sequence falling within the scope of the genus, and for reasons discussed above, the words "PHA synthase," and "Co-A-dependent aldehyde dehydrogenase classify proteins and readily convey distinguishing information concerning identity, via structure and function, such that one of ordinary skill in the art could easily visualize the identity of the members of each classification.

Thus, the Examiner's allegation that the genus comprising aldehyde dehydrogenase and PHA synthase is very large, having different structures, and that the specification teaches the structure of a single CoA-dependent aldehyde dehydrogenase isolated from *E. coli* and the structure of a single PHA synthase isolated from *Aeromonas caviae* is wrong for the reasons set forth above. Secondly, the examiner seems to overlook the fact that Appellants are NOT claiming novel isolated enzymes, but the use and incorporation of these known enzymes (in a novel combination). The individual enzymes having been extensively described and characterized in the art; a patent need not disclose and preferably omits what is already known in the art. Furthermore, if additional enzymes from alternative sources are desirable, one of ordinary skill in the art can find most of the enzymes in the literature, through commercial sources or may isolate the necessary genes using any of a number of techniques, including the use of oligonucleotide primers *designed to be complementary to the known sequence* (and/or degenerate primers) in conjunction with, for example, polymerase chain reaction (PCR). One of ordinary skill in the art will easily recognize that any asserted gaps between the present disclosure and claim breadth can be easily bridged; and will understand that any/all PHA biosynthetic enzymes that fall within each of the identified classes of enzymes (based upon already known amino acid sequence and function) could be used efficiently as reagents for production of glycolic acid-containing PHA polymers. The Examiner is clearly overlooking the Board of Patent Appeals and Interferences' and the Federal Court's emphasis that written description is determined from the perspective of what the specification conveys to one skilled in the art citing *In re GPAC Inc.*, 57 F.3d 1573, 1579, 35 USPQ2d 1116, 1121 (Fed. Cir. 1995) and *Vas Cath*, 935 F.2d at 1563-

64.

With regard to the organisms listed in claim 16, it was well known that a number of different organisms have the cellular machinery to produce polyhydroxyalkanoates, either endogenously, or through genetic engineering. For example, Madison discusses the production of polyhydroxyalkanoates in bacteria (pages 37-40 and 41-44) and other microorganisms (pages 40-41), yeast (page 44), plants (page 45), insect cells (page 45), and animal tissues (page 45).

Applicants note that the Examiner has provided no evidence to contradict Applicant's evidence, only argumentation. Once the applicants' have rebutted the rejection with evidence, the examiner must provide a basis, not argumentation, for why the rejection has been maintained. *The examiner has failed to do so.*

Therefore, claims 16 and 17 meet the written description requirement.

Claims 18, 19, and 20

Claims 18 states that the organism further comprises one or more genes encoding enzymes selected from the group consisting of acyl-CoA transferase, acyl-CoA synthetase, β -ketothiolase, and acetoacetyl-CoA reductase. Claims 19 and 20 require that the gene be homologous or heterologous to the organism. As discussed above for PHA synthase and aldehyde dehydrogenase, these genes are known in the art, and organisms expressing the genes recited in the claims are also known in the art (*See* Madison). As stated in the MPEP §2163 "there is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure." *Falkner v. Inglis*, 448 F.3d 1357, 1366, 79 USPQ2d 1001, 1007 (Fed. Cir. 2006)." See also *Capon v. Eshhar*, 418

F.3d at 1358, 76 USPQ2d at 1084. ("The Board erred in holding that the specifications do not meet the written description requirement because they do not reiterate the structure or formula or chemical name for the nucleotide sequences of the claimed chimeric genes" where the genes were novel combinations of known DNA segments.)". Similarly here, the claims define recombinant organism expressing genes which have already been described in the art. As affirmed by the Court in *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524 (Fed. Cir. 1987), a patent need not teach, and preferably omits, what is well known in the art.

Therefore, claims 18, 19 and 20 meet the written description requirement.

Claim 21

Claim 21 limits the origin of the aldehyde dehydrogenase to *eutE* from *E. coli*. As admitted by the Examiner, the specification teaches the structure of *eutE* from *E. coli* (See the specification at least at page 9, lines 13-23 and from page 16-18). Therefore, claim 21 meets the written description requirement.

Claim 22

Claim 22 specifies that the recombinant organism is a bacteria. Bacteria suitable for production of PHAs are well known to those of skilled in the art and are described in the specification at least from page 1, line 10, until page 3, line 8 (See also, Madison).

Claim 23

Claim 23 specifies that the recombinant organism is a plant. Plants suitable for production of PHAs are well known to those of skilled in the art (See for example, Madison).

(iii) Rejection under 35 U.S.C. § 112, first paragraph, enablement

Claims 16-23 were rejected under 35 U.S.C. § 112, first paragraph, as not enabled.

The Legal Standard

The Court of Appeals for the Federal Circuit (CAFC) has described the legal standard for enablement under § 112, first paragraph, as whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art, without undue experimentation. See, e.g., *Amgen v. Hoechst Marion Roussell* 314 F.3d 1313 (Fed. Cir. 2003) and *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d at 165, 42 USPQ2d at 1004 (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). See also *In re Fisher*, 427 F.2d at 839, 166 USPQ at 24; *United States v. Telectronics, Inc.*, 857 F.2d 778 (Fed. Cir. 1988); and *In re Stephens*, 529 F.2d 1343 (CCPA 1976). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *M.I.T. v. A.B. Fortia*, 774 F.2d 1104 (Fed. Cir. 1985). The adequacy of a specification's description is not necessarily defeated by the need for some experimentation to determine the properties of a claimed product. See *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 323 F.3d 956, 965-966 63 USPQ2d 1609, 1614 (Fed. Cir. 2002). In addition, a patent need not teach, and preferably omits, what is well known in the art. See *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), citing *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 U.S.P.Q. 481, 489 (Fed. Cir. 1984). Thus, information that is conventional or well-known to one of ordinary skill in the art need not be disclosed by the specification.

Whether the disclosure is enabling is a legal conclusion based upon several underlying factual inquiries. See *In re Wands*, 858 F.2d 731, 735, 736-737, 8 USPQ2d 1400, 1402, 1404 (Fed. Cir.1988). As set forth in *Wands*, the factors to be considered in determining whether a claimed invention is enabled throughout its scope without undue experimentation include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. In cases that involve unpredictable factors, "the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation "must not be unduly extensive." *In re Atlas Powder Co., v. E.I. DuPont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir.1984).

As noted in *Ex parte Jackson*, the test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed. *Ex parte Jackson*, 217 USPQ 804, 807 (PTO Bd. App. 1982). There is no requirement for examples. *In re Borkowski*, 422 F.2d 904, 57 C.C.P.A. 946 (C.C.P.A. 1970). Further, patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. *In re Vaeck*, 947 F.2d 488, (Fed. Cir.

1991). As set forth in *Johns Hopkins Univ. v. CellPro Inc.*, 152 F.3d 1342, 1361, 47 USPQ2d 1705, 1714 (Fed. Cir. 1998), "the enablement requirement is met if the description enables any mode of making and using the invention."

The standard defined by the MPEP states:

"Any analysis of whether a particular claim is supported by the disclosure in an application requires a determination of whether that disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention. The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde*, 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Accordingly, even though the statute does not use the term "undue experimentation," it has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988). See also *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988) ("The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation."). A patent need not teach, and preferably omits, what is well known in the art. *In re Buchner*, 929

F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984). Determining enablement is a question of law based on underlying factual findings. *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991); *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984)."

"The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), aff'd. sub nom., *Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985). See also *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). "

Analysis

Claims 16 and 17

The test for enablement is whether the specification teaches a skilled artisan how to make and use the claimed recombinant organisms. The claims define a recombinant organism for producing polyhydroxyalkanoate, selected from the group consisting of bacteria, yeast, fungi and plants, comprising a heterologous gene encoding a CoA-dependent aldehyde dehydrogenase and

a PHA synthase.

Applicants are addressing the problem of how to provide recombinant organisms that can produce *high levels of medium chain length polyhydroxyalkanoates* (see page 3, line 27 to page 4, line 3 and page 8, lines 27-30) while avoiding increasing the level of 3-hydroxyacid in the feed, avoiding the use of 3-propionic acid in the feed, and avoiding the generation of free propionic acid in the cytosol, which in turn reduces the rate of production.

The Examiner alleges that the disclosure is limited to a microorganism comprising the nucleotide and encoded amino acid sequence of only one aldehyde dehydrogenase gene, one acyl-CoA transferase gene, or one acyl-CoA synthetase gene, one β -ketothiolase gene, and acetoacetyl-CoA reductase gene and three PHA synthase genes. It is unclear to Appellants how the Examiner arrived at this conclusion; however, the conclusion is erroneous. As discussed above with respect to the written description requirement and further below, the specification discloses numerous sources for the enzymes recited in the claims. Methods for heterologous expression in all of the organisms recited in claim 1 are known in the art (See Madison, Huisman, or Poirier, et al., *Appl. Environ. Microbiol.* 67(11):5254-60 (2001) ("Poirier", submitted with the amendment and response filed on March 29, 2007, a copy of which is attached to the evidence appendix)). Furthermore, the specification also discloses how to heterologously express specific enzymes for example, in *E. coli*. The examiner has failed to provide any evidence or reasoning as to why those skilled in the art would not extrapolate from the actual examples in the application to other aldehyde dehydrogenase, acyl-CoA transferase, acyl-CoA synthetase, β -ketothiolase, acetoacetyl-CoA reductase and PHA synthase genes from

other sources that are known in the art as evidenced by disclosure in the specification and literature cited and enclosed in this appeal brief.

Sources for CoA-aldehyde dehydrogenase are known in the art and are disclosed in the specification from page 9, line 13, until page 10, line 29 (*See also Poirier or Toth, et al., Appl. Environ. Microbiol.*, 65(11):4973-80 (1999) cited by the Examiner in the office action dated May 11, 2006, a copy of which is attached to the evidence appendix). Genes and techniques for developing recombinant PHA producers are known in the art (*see Madison*). A skilled artisan, from the information in the art, would know which of the disclosed genes to use. For example, U.S. Patent No. 5,534,432 to Peoples' et al ("Peoples" cited in the information disclosure statement filed on Dec, 23, 2003, and considered by the Examiner on June 15, 2006) discloses methods used to isolate genes encoding beta-ketothiolase, acetoacetyl-CoA reductase, PHB polymerase and PHA polymerase (from *Z. ramigera*, *A. eutrophus*, *N. salmonicolor* and *P. oleovorans*), their expression products as well as the sequences regulating their expression. Peoples also discloses how to express these genes in plants. Poirier discloses the expression of PHA biosynthesis genes in yeast and discusses their successful expression in plants, leading to the production of PHAs in these systems. The art is very well developed in the process of expressing the genes recited in the claims (albeit not in the same combination), in the heterologous systems recited in claim 16, with numerous papers published to this effect, and patents issued (See for example Peoples and U.S. Patent No. 6,329,183 to Skraly, et al., cited in the information disclosure statement filed on Dec, 23, 2003, and considered by the Examiner on June 15, 2006). The individual genes that are required to produce the organisms as extensively

discussed are not novel. They have been known in the art over the last twenty years and used for heterologous expression, although not in the combination recited in the claims, which is beneficial in preventing accumulation of 3-hydroxy acid in the cytosol of the PHA producing organism. It is unclear how using genes that are known, with known methods of heterologous expression to make the claimed organisms, cannot be enabled. Furthermore, any mutants and variants of these genes that do not work are outside the scope of these claims, since the claims require that the organism be able to produce PHA. Not only are all the genes to be incorporated into the recombinant organism claimed by the Applicants well known in the art, Applicants have provided numerous working examples of recombinant *E. coli* producing PHA as claimed.

The Examiner alleges that Appellants have not provided a method of making all of the variants or mutants of the *E. coli* CoA-dependent aldehyde dehydrogenase and PHA synthase. Appellants respectfully remind the Examiner that a disclosure of every operable species is not required for the claims to be enabled, even in an unpredictable art (*See* MPEP §2164.03). Furthermore, the Examiners attention is again drawn to the fact that Appellants are not claiming novel genes. The genes are known. A point of novelty here is that Appellants have provided organisms that can produce high levels of medium chain length polyhydroxyalkanoates while avoiding increasing the level of 3-hydroxyacid, by providing the organisms with the ability to also express in combination with the PHA biosynthesis genes, a CoA-dependent aldehyde dehydrogenase, to scavenge 3-hydroxyacids. There is sufficient guidance in the specification to construct plasmids and express the claimed genes (*See* Examples in the pending application). In addition, the experimental protocols are routine and expression vectors, restriction enzymes and

ligation enzymes are commercially available. Thus, one of ordinary skill in the art with the disclosure in the specification, knows what genes to use, and how to make and express the recited genes heterologously. Therefore, claims 16 and 17 are enabled.

Claims 18, 19, and 20

Claims 18 states that the organism further comprises one or more genes encoding enzymes selected from the group consisting of acyl-CoA transferase, acyl-CoA synthetase, β -ketothiolase, and acetoacetyl-CoA reductase. Claims 19 and 20 require that the gene be homologous or heterologous to the organism. As discussed above for PHA synthase and aldehyde dehydrogenase, these genes are known in the art, and organisms express the genes recited in the claims are also known in the art (*See* Madison). Although there is no need for examples, Examples 3-7 describes the production of PHA containing hydroxyvalerate, wherein the organism expresses the genes recited in claim 18. Therefore, claims 18-20 are enabled.

Claim 21

Claim 21 recites all of the limitations of claim 16 and further defines the CoA-dependent aldehyde dehydrogenase to be the *eutE* of *E. coli*. The specification clearly teaches how to make recombinant organisms expressing *eutE* from *E. coli* (See the specification at least from page 16-18, and Examples 4 and 5). Therefore, claim 21 is enabled.

Claim 22

Claims 22 recites all of the limitations of claim 16, and further defines the organism as a bacteria. Bacteria suitable for production of PHAs are well known to those of skill in the art (*See* Madison, pages 37-40 and 41-44). Although there is no need for examples, Examples 3-7

describes the production of PHA containing hydroxyvalerate in *E. coli*. Therefore claim 22 is enabled.

Claim 23

Claim 23 recites all of the limitations of claim 16, and further defines the organism as a plant. Plants that can be used for the production of PHA are known in the art. (See Madison, page 45 and Poirier). The genes recited in the claims to be heterologously expressed in the plants are not only known in the art, they are disclosed in the specification. Thus, it would be easy for one of ordinary skill in the art, using knowledge in the art and Appellants discovery of the requisite combination of genes necessary to avoid accumulation of propionic acid in the cytosol, to make the claimed organisms. Therefore, claims 23 is enabled.

(8) Conclusion

The claims define organisms expressing genes whose sequences are known, in a novel combination that avoids the accumulation of propionic acid in the cytosol of PHA-producing organisms, to solve a long standing problem in the field. Not only are the individual genes known, they have been heterologously expressed in other systems. Methods for heterologous expression are known in the art, and the specification provides numerous examples. The claims are not drawn to novel genes. The determination of compliance with written description and enablement must be made in light of what is known in the art. From the disclosure in the specification and what is known in the art, claims 16-23 clearly meet the written description and enablement requirements.

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For the foregoing reasons, Appellants submits that claims 16-23 are patentable.

Respectfully submitted,

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Claims Appendix: Claims On Appeal

1. (Withdrawn) A method of producing polyhydroxyalkanoates (PHA) polymer comprising at least one monomer selected from the group consisting of 3-hydroxypropionate, 3-hydroxyvalerate, 4-hydroxybutyrate, 4-hydroxyvalerate, 5-hydroxyvalerate, and 3-hydroxyhexanoate, comprising
expressing in an organism genes encoding a polyhydroxyalkanoate (PHA) synthase and a CoA-dependent aldehyde dehydrogenase, wherein at least one gene is a heterologous gene, and feeding an alcohol to the organism.
2. (Withdrawn) The method of claim 1 wherein the PHA polymer further comprises 3-hydroxybutyrate.
3. (Withdrawn) The method of claim 1 wherein the PHA polymer is selected from the group consisting poly-3-hydroxybutyrate-co-3-hydroxyvalerate, poly-3-hydroxybutyrate-co-3-hydroxypropionate, poly-3-hydroxybutyrate-co-4-hydroxybutyrate, poly-3-hydroxybutyrate-co-3-hydroxyheanoate.
4. (Withdrawn) The method of claim 1 wherein the alcohol is selected from the group consisting of 1-propanol, 1,2-propanediol, and 1-butanol.
5. (Withdrawn) The method of claim 1 wherein the genes further encode enzymes selected from the group consisting of acyl-CoA transferase, acyl-CoA synthetase, β -ketothiolase, acetoacetyl-CoA reductase.
6. (Withdrawn) The method of claim 1 wherein the organism is selected from the group consisting of yeast, bacteria, fungi, and plants.

7. (Withdrawn) The method of claim 1 wherein the PHA synthase is poly(3-hydroxyalkanoate) synthase.

8. (Withdrawn) The method of claim 1 wherein the PHA synthase is poly(4-hydroxyalkanoate) synthase.

9. (Withdrawn) The method of claim 8 wherein the PHA synthase is poly(4-hydroxybutyrate) synthase.

10. (Withdrawn) The method of claim 1 wherein the organism is a bacterium.

11. (Withdrawn) The method of claim 10 wherein the organism is *E. coli*.

12. (Withdrawn) The method of claim 1 wherein the organism is *E. coli* expressing the *E. coli eutE* gene.

Claims 13-15 (cancelled)

16. (previously presented) A recombinant organism selected from the group consisting of bacteria, yeast, fungi and plants for producing polyhydroxyalkanoates, comprising a heterologous gene encoding a CoA-dependent aldehyde dehydrogenase and a PHA synthase.

17. (previously presented) The recombinant organism of claim 16 further comprising a heterologous gene encoding a PHA synthase.

18. (previously presented) The recombinant organism of claim 17 further comprising one or more genes, wherein the genes encode enzymes selected from the group consisting of acyl-CoA transferase, acyl-CoA synthetase, β -ketothiolase, acetoacetyl-CoA reductase.

19. (Original) The recombinant organism of claim 18, wherein one or more of the genes are endogenous to the recombinant organism.

20. (Original) The recombinant organism of claim 18, wherein one or more of the genes encoding enzymes selected from the group consisting of acyl-CoA transferase, acyl-CoA synthetase, β -ketothiolase, acetoacetyl-CoA reductase are heterologous to the recombinant organism.
21. (Original) The recombinant organism of claim 16 wherein the gene is *eutE* of *E. coli*.
22. (Original) The recombinant organism of claim 16 which is a bacteria.
23. (Original) The recombinant organism of claim 16 which is a plant.
24. (Withdrawn) A method of producing polyhydroxyalkanoate (PHA) polymers comprising at least one monomer selected from the group consisting of 3-hydroxypropionate, 3-hydroxyvalerate, 4-hydroxybutyrate, 4-hydroxyvalerate, 5-hydroxyvalerate, and 3-hydroxyhexanoate, comprising
selecting an organism selected from the group consisting of bacteria, yeast, fungi and plants, genetically engineered to express a CoA-dependent aldehyde dehydrogenase and a PHA synthase, and feeding an alcohol to the organism.
25. (Withdrawn) The method of claim 24 wherein the PHA polymer further comprises 3-hydroxybutyrate.
26. (Withdrawn) The method of claim 24 wherein the PHA polymer is selected from the group consisting poly-3-hydroxybutyrate-co-3-hydroxyvalerate, poly-3-hydroxybutyrate-co-3-hydroxypropionate, poly-3-hydroxybutyrate-co-4-hydroxybutyrate, poly-3-hydroxybutyrate-co-3-hydroxyheanoate.

27. (Withdrawn) The method of claim 24 wherein the alcohol is selected from the group consisting of 1-propanol, 1,2-propanediol, and 1-butanol.
28. (Withdrawn) The method of claim 24 wherein the organism comprises genes encoding enzymes selected from the group consisting of acyl-CoA transferase, acyl-CoA synthetase, β -ketothiolase, acetoacetyl-CoA reductase.
29. (Withdrawn) The method of claim 24 wherein the organism is selected from the group consisting of bacteria and plants.
30. (Withdrawn) The method of claim 24 wherein the PHA synthase is poly(3-hydroxyalkanoate) synthase.
31. (Withdrawn) The method of claim 24 wherein the PHA synthase is poly(4-hydroxyalkanoate) synthase.
32. (Withdrawn) The method of claim 31 wherein the PHA synthase is poly(4-hydroxybutyrate) synthase.
33. (Withdrawn) The method of claim 24 wherein the organism is a bacterium.
34. (Withdrawn) The method of claim 33 wherein the organism is *E. coli*.
35. (Withdrawn) The method of claim 24 wherein the organism is *E. coli* expressing the *E. coli eutE* gene.

Claims 36-38 (cancelled)

Evidence Appendix

I. Reference Cited in the Information Disclosure Statement filed in December 23, 2003

Madison and Huisman, *Microbiol. Mol. Biol. Rev.*, 63:21-53 (1999)

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Poirier, et al., *Appl. Environ. Microbiol.*, 67(11):5254-60 (2001)

III. Reference Cited By the Examiner in the Office action mailed on May 11, 2006

Toth, et al., *Appl. Environ. Microbiol.*, 65(11):4973-80 (1999)

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Related Proceedings Appendix

None